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Original Article

Time structure of leg movement activity during sleep in untreated Parkinson disease and effects of dopaminergic treatment

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ABSTRACT

Objectives: To evaluate the specific time structure of periodic leg movements during sleep (PLMS) in untreated Parkinson disease (PD) patients by means of an advanced analysis; and to evaluate the effects of treatment on this activity, in a cross-sectional comparison and in a prospective follow-up study, in a subgroup of previously untreated patients.

Methods: Forty-four consecutive PD patients were enrolled in the study; 19 had not yet started any drug therapy for PD (PDnother); 10 out of these patients were re-evaluated after an average time lag of 19.6 months from baseline. The remaining 25 patients (PDther) were taking L-dopa and/or dopamine agonists. Eighteen age-matched normal controls were also included. All subjects underwent a polysomnographic recording and the time structure of their sleep leg movement activity was analyzed by means of the periodicity index and other advanced measures.

Results: Both PD groups tended to show increased PLMS and decreased isolated limb movement activity with respect to controls. PLMS index >15/h was found in 26.3% of PDnother patients, 24.0% of PDther subjects, and in 16.7% of controls; none of the three PDnother patients who had PLMS index >15/h at baseline sustained this level at follow-up, nor did the other seven patients. The intermovement interval distribution showed a clear peak at 10–40 s in the PDnother group; a suppression of this peak was observed after the introduction of dopaminergic treatment in the subgroup of 10 PDnother patients. Both groups of PD patients showed a progressively decreasing number of PLMS through the night; an almost complete abolition of PLMS was seen in the first 2 h of sleep after the introduction of dopaminergic drug therapy.

Conclusion: Our data do not seem to support the hypothesis that PLMS are particularly frequent in PD but seem to indicate an interaction between PD pathophysiology and genetic predisposition for PLMS, producing a slightly increased number of patients with this sleep motor phenomenon when compared to controls.

1. Introduction

The presence of sleep disorders in Parkinson disease (PD) was reported by James Parkinson in 1817 when he published "An essay on the shaking palsy" [1]. At least three-quarters of PD patients have sleep problems: two-thirds of them have problems in initiating sleep; difficulties maintaining sleep are reported by nine out of ten; and 50% spontaneously refer sleep problems [2,3]. The most frequent sleep disturbances in PD are difficulty initiating sleep, frequent night-time awakening and sleep fragmentation, nocturia, restless legs syndrome (RLS)/periodic limb movements during sleep (PLMS), sleep breathing disorders, drug-induced symptoms, narcolepsy-like features, sleep attacks and excessive daytime sleepiness, and parasomnias associated with rapid eye movement (REM) sleep [2].

Some past studies have indicated that periodic leg movements during sleep (PLMS) are especially increased in PD [4,5]; a more recent review of case–control studies of sleep in PD [6] has listed two studies confirming this increase [7,8] and five which did not find changes [9–13]. However, their analysis has been based on

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the computation of the PLMS index (number of PLMS/h of sleep) alone. This measure is largely insufficient to describe the real periodicity of the leg movement activity during sleep and is unspecific [14]. In recent years, a more advanced approach has enabled a more accurate description of periodicity and other time-structure features of leg movements during sleep in RLS [15–17] and other clinical conditions in which PLMS have been reported, such as REM sleep behavior disorder (RBD) [18], narcolepsy [19], and insomnia [20]. The application of this method has found significant differences between the different clinical conditions that the PLMS index alone failed to detect [14] and has enabled assessment of the effects of drug therapy with great accuracy [21,22].

For the reasons listed above, the aims of this study were: (i) to evaluate the specific time structure of PLMS in untreated PD patients by means of an advanced analysis; (ii) and to evaluate the effects of treatment on this activity in a cross-sectional comparison first, and, in a prospective follow-up study, in a subgroup of previously untreated patients.

2. Methods

2.1. Subjects

Forty-four consecutive PD patients were enrolled in the study [28 men and 16 women; mean (SD) age, 67.6 (7.0) years]. All patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD [23]. Exclusion criteria were: presence of other neurological diseases, Mini-Mental State Examination score <20 [24], and presence of a psychiatric disease according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) [25]. The Hoehn & Yahr (H&Y) disease stage was assessed for each patient [26] and disease duration was carefully evaluated.

Nineteen patients had not yet started any drug therapy for PD (PDnother subgroup), including 11 males and eight females [mean (standard deviation) age, 67.6 (6.2) years]. Ten of these patients (seven males and three females), were re-evaluated after an average time lag of 19.6 (10.8) months from the first (baseline) assessment; the remaining nine patients refused the second polysomnographic night recording or were unavailable.

The remaining 25 patients [17 men and eight women; mean age, 67.6 (7.7) years] constituted the PDther subgroup and were taking L-dopa monotherapy, dopamine agonist alone, or a combination of the two. In order to evaluate different dopaminergic treatments, drug dosages were converted to L-dopa dosage equivalents (LEDs), according to Tomlinson et al. [27]. None of the patients was taking antidepressants and only two of them were taking clonazepam at bedtime; however, this substance does not seem to affect PLMS [28].

A careful diagnosis of RBD was also carried out, based on the International Classification of Sleep Disorders, 2nd ed. [29] criteria for RBD, and including the presence of REM sleep without atonia, sleep-related injurious–disruptive behaviors by history or abnormal sleep behaviors documented during polysomnographic monitoring, and absence of electro-encephalographic (EEG) epileptiform activity during REM sleep. Also the presence of RLS was assessed following standard criteria [29].

The control group was formed by 18 age-matched normal controls [11 men and seven women aged 66.9 (8.1) years]. The exclusion criteria for the control group were the same as described for PD patients; additionally, the presence of subjective sleep complaints (insomnia, daytime sleepiness, RLS, RBD symptoms, snoring, or witnessed apnea) was also ruled out. None of the controls was taking hypnotics or benzodiazepines.

This study was approved by the local ethics committee and all subjects provided informed consent according to the Declaration of Helsinki before entering the study.

2.2. Polygraphic sleep recordings

Each subject underwent a full polysomnographic night recording, after an adaptation night, carried out in a standard sound-attenuated (noise level to a maximum of 30 dB nHL) sleep laboratory. Subjects were not allowed to have beverages containing caffeine during the afternoon preceding the recording and were allowed to sleep until their spontaneous awakening in the morning.

The following parameters were included in the polysomnographic study: EEG (at least three channels – one frontal, one central, and one occipital – referred to the contralateral earlobe); electro-oculogram (electrodes placed 1 cm above the right outer cantus and 1 cm below the left outer cantus and referred to A1), electromyogram (EMG) of the submentalis muscle, EMG of the right and left tibialis anterior muscles (bipolar derivations with two electrodes placed 3 cm apart on the belly of the anterior tibialis muscle of each leg), and electrocardiogram (one derivation). The sleep respiratory pattern of each patient was assessed by means of oral and nasal airflow (thermistor and/or nasal pressure cannula), thoracic and abdominal respiratory effort (strain gauge), and oxygen saturation (pulse-oximetry) in a previous recording (within one week) or during the study night. Sleep signals were stored on hard disk in European data format for further analysis.

2.3. Sleep scoring and detection of limb movements

Sleep stages were scored following standard criteria [30] on 30 s epochs by means of the sleep analysis software Hypnolab 1.2 (SWS Soft, Italy). Leg movements (LMs) during sleep were first detected by the same software. With this software, the detection is performed by means of a human-supervised automatic approach controlled by the scorer. The performances of this system have been evaluated and validated [31]; for this study, one scorer (R.F.) visually edited the detections proposed by the automatic analysis before the computation of the LM parameters, which were automatically generated by the same software, adopting the criteria set by the International RLS Study Group and endorsed by the World Association of Sleep Medicine [32]. The PLMS index was calculated as the number of LMs included in a series of four of more, separated by >5 s and <90 s, per hour of sleep. Additionally, the number of intermovement intervals of 10–90 s, all in sequences of at least three, was divided by the total number of intervals to yield the periodicity index; this index can vary between 0 (absence of periodicity, with none of the intervals being 10–90 s) and 1 (complete periodicity, with all intervals being 10–90 s) [15,33]. The periodicity index is independent of the absolute number of LMs recorded and calculated for all nights included in this study.

2.4. Statistical analysis

All comparisons were performed using one-way analysis of variance (ANOVA), followed by the least significant difference test for post-hoc analyses, or by Student's *t*-test for paired datasets, as appropriate. However, because of the limited number of subjects available for the follow-up analysis, and to rule out possible type II errors, we also calculated effect sizes using Cohen's *d*-value which is defined as the difference between two means divided by their pooled standard deviation. According to Cohen, 0.2 indicates a small effect, 0.5 a medium effect, and $\geqslant$0.8 a large effect. The χ^2-test was used for the comparison of frequencies. The commercially available Statistica software package (StatSoft, Inc., 2001;

Statistica data analysis software system, version 6. www.statsoft.com) was used. Differences were considered significant at $P < 0.05$.

3. Results

Age and sex composition of the three groups of subjects were not different in the one-way ANOVA and χ^2-square test, respectively. Mean (standard deviation) disease duration was longer in the PDther group than in the PDnother group [4.6 (3.9) vs 1.4 (0.7) years, respectively; $P < 0.0016$]; mean H&Y stage was higher [1.9 (0.7) vs 1.2 (0.36), respectively; $P < 0.001$], whereas the average MMSE was not significantly different [27.5 (3.3) vs 28.6 (1.81), respectively]. Mean LEDs in the PDther group were 464.6 (379.4) whereas at follow-up in the PDnother group they were 335.9 (112.1) and H&Y had increased significantly [1.6 (0.6), $P < 0.024$].

Sixteen patients in the PDther group and 17 in the PDnother group were also affected by RBD; only two patients in the PDther group had symptoms of RLS; and an apnea/hypopnea index (AHI) >15/h was found in three patients of each PD subgroup. However, LMs were not associated with respiratory events [32] in these subjects. None of these subjects was under ventilatory treatment because a diagnosis of sleep apnea had not been determined previously. None of the 10 PDnother group who underwent a follow-up assessment had AHI >15/h.

3.1. Sleep architecture

The sleep scoring parameters found in the three groups of subjects are reported in Table 1. PD patients under treatment had sleep period time shorter than controls; total sleep time was longest in controls and shortest in PDther patients, with PDnother showing intermediate values. Sleep efficiency was significantly decreased in PDther patients who showed the lowest values; the opposite was evident for wakefulness after sleep onset, which was highest in these patients. Sleep stage 2 was reduced in PDther patients vs controls while slow wave sleep appeared to be reduced only in the PDther group vs PDnother patients.

The subgroups of PDnother patients who were re-evaluated after an average time lag of 19.6 months, during which dopaminergic therapy was administered, showed an increase in time in bed (with a marginal statistical significance which would not pass a correction for multiple comparisons but with a large effect size), an increase in REM sleep latency, and a decrease in slow wave sleep (Table 2).

3.2. Leg movements during sleep

The parameters derived from the analysis of the LM activity during sleep in the three groups of subjects is reported in Table 3. Both PD groups tended to show increased PLMS and decreased isolated LM activity with respect to controls; however, statistical

Table 1
Sleep scoring parameters of the three groups of subjects.

	A. Controls ($n = 18$)		B. PDnother ($n = 19$)		C. PDther ($n = 25$)		ANOVA P	Post-hoc P		
	Mean	SD	Mean	SD	Mean	SD		A vs B	A vs C	B vs C
TIB (min)	504.5	58.8	456.9	89.7	452.4	64.1	NS			
SPT (min)	485.5	63.5	433.9	87.5	410.2	76.9	<0.024	NS	<0.0066	NS
TST (min)	403.5	57.1	343.1	88.6	282.6	78.7	<0.00013	<0.036	<0.00003	<0.014
SL (min)	14.6	12.6	20.6	24.5	28.7	38.1	NS			
FRL (min)	102.9	89.4	106.0	89.4	154.8	89.9	NS			
Stage shifts/h	12.5	3.5	16.7	4.3	14.1	6.8	NS			
Awakenings/h	6.4	2.9	7.9	3.1	8.3	5.3	NS			
SE (%)	80.1	7.6	74.9	12.3	62.9	17.0	<0.001	NS	<0.0006	<0.006
WASO (%)	16.5	9.2	21.3	11.1	30.9	16.3	<0.0055	NS	<0.0026	<0.022
S1 (%)	6.0	3.3	8.0	3.4	9.6	7.0	NS			
S2 (%)	47.0	10.0	39.0	9.4	37.3	13.2	<0.046	NS	0.015	NS
SWS (%)	16.0	8.4	19.7	9.5	11.7	8.5	<0.017	NS	NS	<0.0046
REM (%)	14.5	3.4	12.0	6.8	10.4	5.7	NS			

PD, Parkinson disease; nother, no therapy; ther, therapy; ANOVA, analysis of variance; SD, standard deviation; TIB, time in bed; SPT, sleep period time; TST, total sleep time; SL, sleep latency; FRL, first REM latency; SE, sleep efficiency; WASO, wake after sleep onset; S1–2, sleep stages; SWS, slow wave sleep; REM, rapid eye movement.

Table 2
Sleep scoring parameters in the subgroup of PDnother patients ($n = 10$) with follow-up after treatment.

	Baseline		Treatment		t-Test P	Effect size
	Mean	SD	Mean	SD		Cohen's d (95% CI)
TIB (min)	439.7	89.4	525.0	69.9	<0.05	−1.063 (−2.000 to −0.127)
SPT (min)	424.9	85.1	499.7	59.8	NS	−1.017 (−1.949 to −0.086)
TST (min)	351.3	87.9	370.9	69.8	NS	−0.247 (−1.127 to 0.633)
SL (min)	13.6	19.4	11.9	11.3	NS	0.107 (−0.770 to 0.984)
FRL (min)	82.0	62.5	185.2	99.1	<0.0095	−1.246 (−2.204 to −0.288)
Stage shifts/h	17.3	4.4	18.8	4.6	NS	−0.331 (−1.214 to 0.551)
Awakenings/h	8.6	2.9	10.2	3.3	NS	−0.514 (−1.405 to 0.377)
SE (%)	78.9	9.4	71.1	12.1	NS	0.721 (−0.183 to 1.626)
WASO (%)	18.5	8.2	25.6	12.0	NS	−0.690 (−592 to 0.212)
S1 (%)	8.1	2.37	11.7	9.1	NS	−0.539 (−1.431 to 0.353)
S2 (%)	39.9	8.9	38.5	13.4	NS	0.123 (−0.754 to 1.000)
SWS (%)	20.7	9.0	13.3	7.3	<0.014	0.902 (−0.018 to 1.822)
REM (%)	12.8	8.7	10.9	5.7	NS	0.258 (−0.622 to 1.138)

PD, Parkinson disease; nother, no therapy; SD, standard deviation; CI, confidence interval; TIB, time in bed; SPT, sleep period time; NS, not significant; TST, total sleep time; SL, sleep latency; FRL, first REM latency; SE, sleep efficiency; WASO, wake after sleep onset; S1–2, sleep stages; SWS, slow wave sleep; REM, rapid eye movement.

Table 3
Leg movement parameters of the three groups of subjects.

	A. Controls (n = 18)		B. PDnother (n = 19)		C. PDther (n = 25)		ANOVA P	Post-hoc P		
	Mean	SD	Mean	SD	Mean	SD		A vs B	A vs C	B vs C
Total sleep										
Total, index	18.5	8.6	22.9	38.6	22.4	33.0	NS			
PLMS, index	9.7	8.8	18.1	38.1	14.5	30.7	NS			
Isolated, index	8.7	2.8	4.8	3.3	7.9	4.9	0.009	0.0049	NS	0.012
NREM sleep										
Total, index	19.9	9.9	23.8	43.0	22.1	35.9	NS			
PLMS, index	11.5	10.2	19.5	43.1	14.6	33.4	NS			
Isolated, index	8.4	3.5	4.3	3.1	7.5	5.0	0.01	0.0050	NS	0.015
REM sleep										
Total, index	12.2	6.0	16.4	22.3	22.4	23.5	NS			
PLMS, index	2.0	3.3	9.8	18.4	12.1	20.3	NS			
Isolated, index	10.2	3.78	6.6	6.1	10.3	9.1	NS			
PLMS sequence number	5.6	4.35	4.7	7.3	5.1	6.6	NS			
PLMS sequence duration (s)	65.5	107.4	38.7	112.4	60.5	111.1	NS			
PLMS duration in REM (s)	2.3	1.5	1.4	1.6	1.4	1.4	NS			
PLMS duration in NREM (s)	2.0	0.6	2.2	1.0	2.1	1.0	NS			
Isolated LM duration in REM (s)	2.4	0.8	1.8	1.3	1.4	1.1	0.026	NS	0.007	NS
Isolated LM duration in NREM (s)	1.9	0.49	2.2	1.1	2.3	0.7	NS			
Periodicity index, total sleep	0.542	0.298	0.255	0.295	0.358	0.287	0.019	0.005	NS	NS
Periodicity index, NREM	0.564	0.303	0.252	0.316	0.330	0.315	0.014	0.0047	NS	0.024
Periodicity index, REM	0.209	0.261	0.101	0.196	0.260	0.304	NS			

PD, Parkinson disease; nother, no therapy; ther, therapy; ANOVA, analysis of variance; SD, standard deviation; NS, not significant; PLMS, periodic limb movements during sleep; NREM, non-REM; REM, rapid eye movement.

significance was reached only for the number of isolated movements of the PDnother group during non-REM (NREM) sleep (and total sleep). PLMS index >15/h was found in five (26.3%) of PDnother patients, in six (24.0%) of PDther subjects, and in three (16.7%) controls (χ^2 = 0.541, not significant); none of the PDnother subgroup patients had PLMS index >15/h at follow-up. Only one patient with PLMS index >15/h in the PDther group was affected by RLS; the remaining subjects with PLMS in both patient groups had no RLS nor sleep apnea. Periodicity index was lowest in PDnother patients. Even if a clear decrease was observed in PLMS in the subgroup of PDnother patients who were re-evaluated after dopaminergic treatment, the differences were not statistically significant (Table 4); however, effect size was medium for total and PLMS index, during both NREM and REM sleep, as well as for the decrease in number of PLMS sequences and duration. A medium effect size was found also for the reduction in duration of isolated LMs and for the periodicity index.

Fig. 1 (upper panel) shows the intermovement interval distribution in the three groups of subjects included in this study. A peak extends from ~10 to 40 s, most notably in the graph of the PDnother group, preceded by a much smaller peak at ~4 s. The peak at 20 s is much smaller, even if discernible, in the PDther group and not very different from that of controls. No significant differences were found, probably due to the large within-group variability of data

Table 4
Leg movement parameters in the subgroup of Parkinson disease–no therapy patients (n = 10) with follow-up after treatment.

	Baseline		Treatment		t-Test P	Effect size
	Mean	SD	Mean	SD		Cohen's d (95% CI)
Total sleep						
Total, index	20.9	36.27	6.2	6.43	NS	0.564 (−0.329 to 1.458)
PLMS, index	16.0	35.94	2.3	3.19	NS	0.537 (−0.355 to 1.429)
Isolated, index	4.9	2.74	4.0	3.86	NS	0.269 (−0.612 to 1.149)
NREM sleep						
Total, index	21.9	42.17	5.7	6.07	NS	0.538 (−0.354 to 1.430)
PLMS, index	17.4	42.68	2.0	3.47	NS	0.509 (−0.382 to 1.399)
Isolated, index	4.5	2.97	3.7	3.67	NS	0.240 (−0.640 to 1.119)
REM sleep						
Total, index	19.0	27.18	8.2	9.78	NS	0.529 (−0.363 to 1.420)
PLMS, index	13.6	23.94	3.0	5.68	NS	0.609 (−0.287 to 1.506)
Isolated, index	5.5	3.96	5.1	5.69	NS	0.082 (−0.795 to 0.958)
PLMS sequence number	5.4	8.96	2.0	2.94	NS	0.510 (−0.381 to 1.400)
PLMS sequence duration (s)	63.6	152.58	4.8	10.21	NS	0.544 (−0.349 to 1.436)
PLMS duration in REM (s)	1.7	1.75	1.0	1.08	NS	0.481 (−0.408 to 1.370)
PLMS duration in NREM (s)	2.3	0.72	1.9	1.72	NS	0.303 (−0.578 to 1.185)
Isolated LM duration in REM (s)	2.0	1.23	1.2	1.08	NS	0.691 (−0.211 to 1.593)
Isolated LM duration in NREM (s)	2.5	1.05	1.5	1.11	NS	0.926 (0.003 to 1.848)
Periodicity index, total sleep	0.248	0.296	0.124	0.182	NS	0.505 (−0.386 to 1.395)
Periodicity index, NREM	0.247	0.305	0.104	0.172	NS	0.578 (−0.318 to 1.472)
Periodicity index, REM	0.127	0.255	0.139	0.252	NS	−0.047 (−0.924 to 0.829)

SD, standard deviation; CI, confidence interval; NS, not significant; PLMS, periodic limb movements during sleep; NREM, non-REM; LM, limb movement; REM, rapid eye movement.

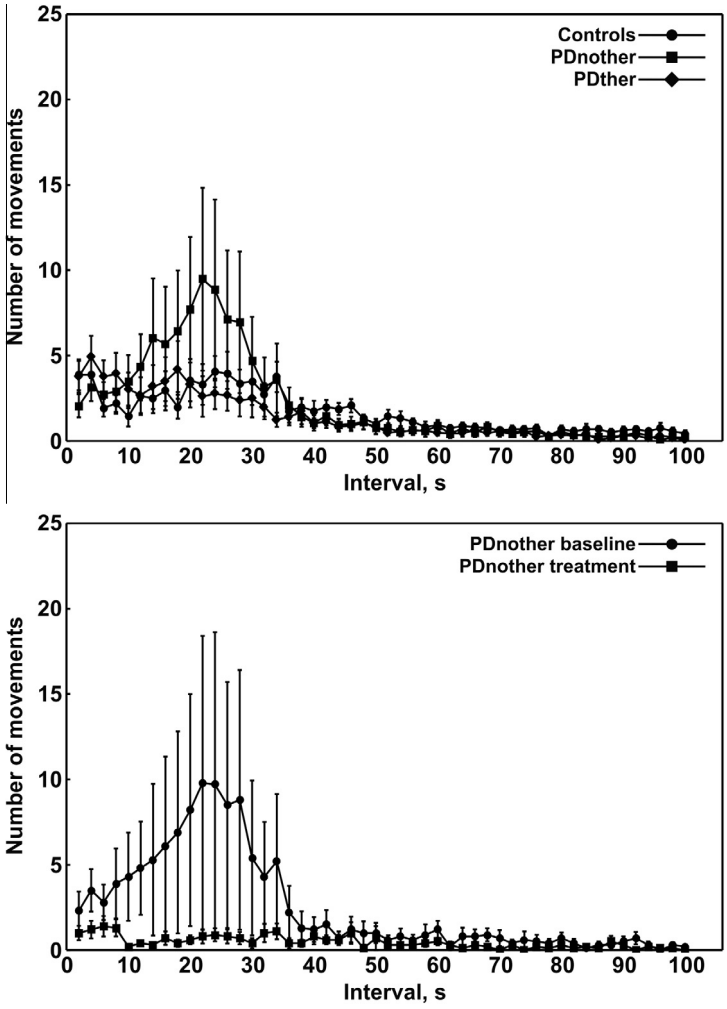

Fig. 1. Intermovement interval distribution in the three groups of subjects included in this study (upper panel) and the in the subgroup of PDnother patients at baseline and after treatment with dopaminergic drug therapy (lower panel). PD, Parkinson disease; nother, no therapy; ther, therapy.

(Fig. 2). Nevertheless, a suppression of this peak was observed after the introduction of dopaminergic treatment in the subgroup of 10 PDnother patients at follow-up (Fig. 1, lower panel).

The distribution of PLMS through the night is shown in Fig. 3. Controls showed an increasing number of PLMS during the first 4 h of sleep, followed by a reduction; both groups of PD patients showed an irregular but progressively decreasing pattern. Isolated LMs showed a stable number throughout the night. The effect of the introduction of dopaminergic treatment in the PDnother subgroup is shown in Fig. 4. At follow-up, there was an almost complete abolition of PLMS in the first 2 h of sleep, followed by a small peak in the following hours. Isolated movements appeared to be marginally modified.

4. Discussion

The results obtained in this study regarding sleep structure in PD are in agreement and confirm earlier reports showing important sleep-stage changes in this condition [6,10] that might not benefit significantly from the dopaminergic drug therapy [34,35], usually adjusted carefully to cover the period of wakefulness. Despite the use of drugs, the PDther group had more important sleep changes than those of the PDnother group, perhaps indicating that disease duration and severity stage were more important factors associated with sleep disruption in these patients. This idea is further reinforced by the substantial lack of beneficial effects found after the introduction of dopaminergic drug therapy in the subgroup of 10 PDnother patients who showed a decrease in slow wave sleep and a significant prolongation of the latency of REM sleep. In this respect, it should also be said that notwithstanding the presence of RBD in several patients, only two of them had taken clonazepam at bedtime; it may be argued that the use of this drug might improve some sleep parameters – as reported for RBD patients [36,37] – but our data do not enable further speculation.

The main focus of our study was the analysis of the time structure of leg movements during sleep: in this respect we found a non-significantly increased amount of PLMS in PD patients (treated and untreated); however, this increase was not particularly high at the group level and involved approximately only one-quarter of the patients. On the contrary, PLMS are detected in 80–90% of all patients with RLS [14,38], another condition in which dopamine probably has a key role [39]. Notwithstanding the recent report that severe RLS may be an early feature of PD [40], the association between these two clinical conditions is weak; most patients with RLS are generally not prone to develop PD during their lifetime and some research results are against a strict association between the two clinical entities. Neurodegeneration involves substantia nigra in PD [41] but not in RLS, and no Lewy bodies are found in RLS brains [42]. Dopamine transporter imaging has shown contrasting

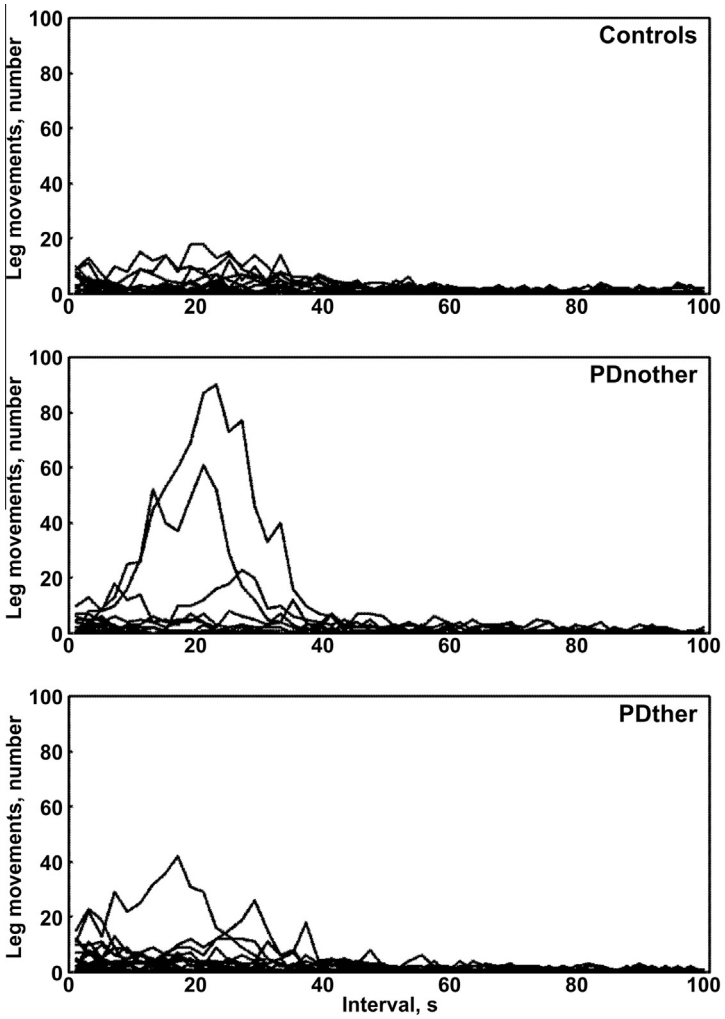

Fig. 2. Individual intermovement interval distributions in the three groups of subjects included in this study. PD, Parkinson disease; nother, no therapy; ther, therapy.

results in RLS [43–45] and abnormal values in PD [46]. Iron content, detected by transcranial ultrasounds, in the substantia nigra is decreased in RLS [47,47] and increased in PD. Finally, there have been no reports so far that the disease-specific genetic loci of one disease are associated with those of the other [48,49].

The low increase in PLMS in PD patients would have been even lower if we had found some control subjects with these movements; it is known that PLMS become more frequent with increasing age, after the age of 40 years [50]. It should be noted that this increase is not found in all controls – only in a minority of them – and it may be happen that in a relatively small sample, such as our group of controls, none has definitive PLMS.

However, the features of PLMS in a subsample of our PD patients (seven out of 44 in total had both PLMS index >15/h and periodicity index >0.5) show some similarities to those of RLS patients. First, the presence of a clear peak at ~20 s in the intermovement interval histogram, preceded by a smaller one at ~4 s; this histogram resembles very closely that of RLS and PLMS disorder (PLMD) patients [14,15,20]. The similarity with PLMS in RLS/PLMD is further supported by the gradually decreasing course during the night [14,15] and by the positive response to dopaminergic treatment [21,51,52]. Regarding this last point, we acknowledge that this part of our study was underpowered, because we were able to obtain a second polysomnograph in only 10 PDnother patients. Despite this limitation and the lack of statistical significance, a trend towards reduction in PLMS due to therapy is evident in Table 4 (supported to some extent by the effect sizes found) and in the graphical data. In this respect, it should be noted that the effect size is specific to the population, independent of experimental details such as sample size. In an underpowered study such as ours, it may indicate comparisons likely to become significant if a larger sample size is achieved. For the moderate effect size values reported in Table 4, a sample size of 25–35 patients might have produced several significant differences.

Of particular interest is the modification induced by the introduction of therapy in the subgroup of PDnother patients on the night course of PLMS. An almost complete abolition was observed during the first 2 h of sleep, followed by a small reappearance of activity in the second half of the night. The effect of L-dopa, the most frequently used drug in our patients, on PLMS in RLS is well known [53] and the reduction time course seen in our PDnother patients is in agreement with the pharmacokinetics of this substance [54]. Additionally, we did not find this early night PLMS abolition in our PDther patients who had longer disease duration and more severe H&Y stage. This might indicate that, similar to other sleep abnormalities, sleep LMs become less responsive to dopaminergic treatment with advancing disease stages [34,35]. This might be due to the fact that this activity is somewhat different from that of untreated early stage PD patients and that it has time structure features different from those of the genuine dopamine agonist responsive PLMS [21] (Fig. 1).

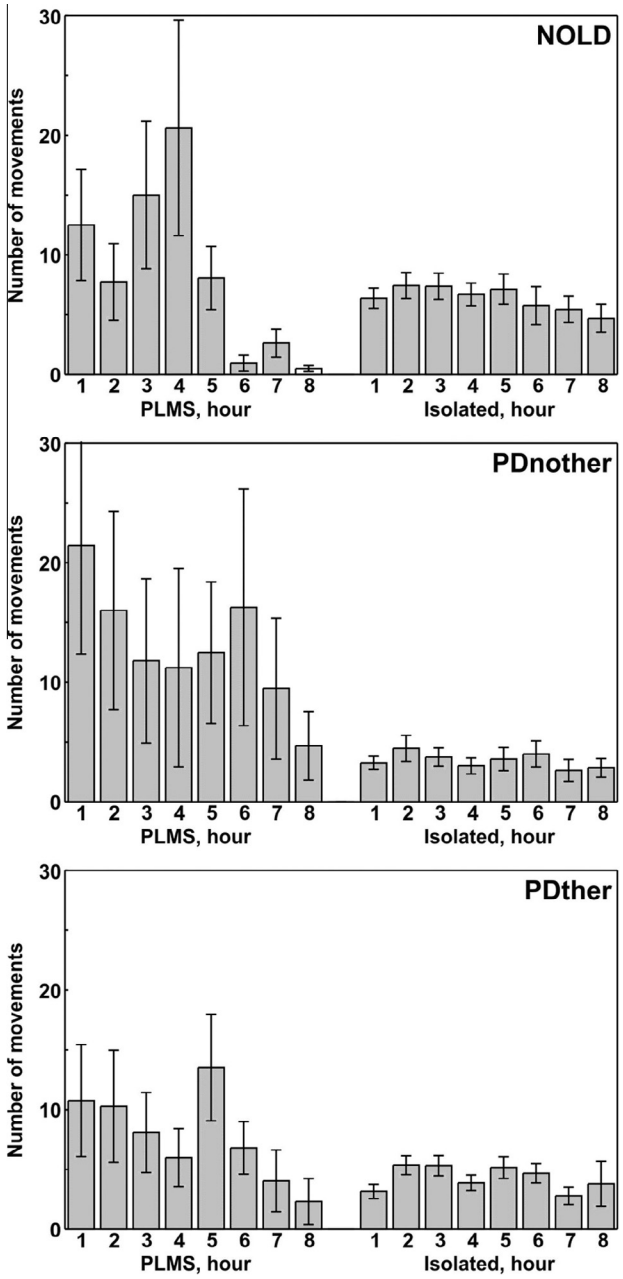

Fig. 3. Distribution of the number of periodic limb movements during sleep (PLMS) and isolated limb movements per hour of the night in the three groups of subjects included in this study.

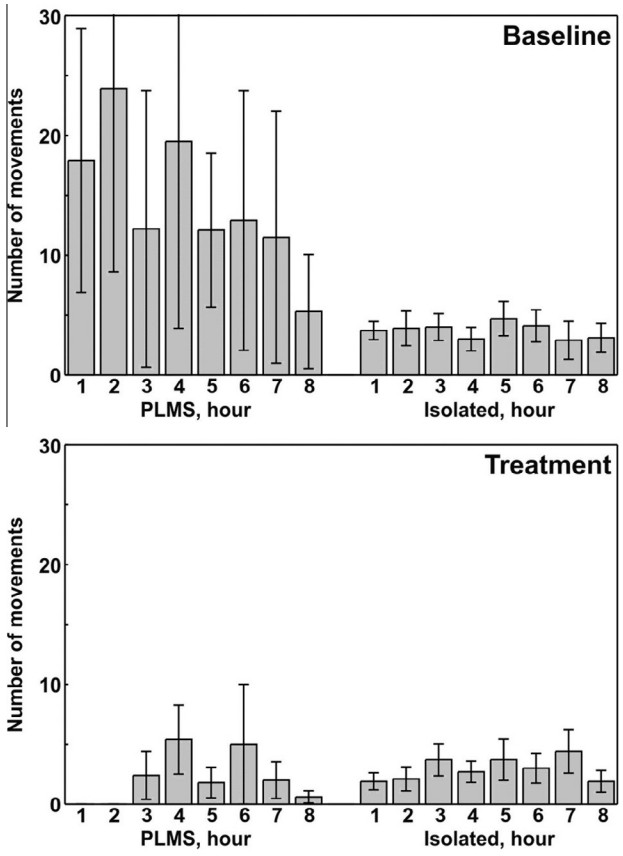

Fig. 4. Distribution of the number of periodic limb movements during sleep (PLMS) and isolated limb movements per hour of the night in the subgroup of Parkinson disease–no therapy patients at baseline and after treatment with dopaminergic drug therapy.

Thus, we have found that untreated early stage PD patients show PLMS with a non-significantly higher frequency than do controls. However, almost three-quarters of them do not have PLMS, whereas treated PD patients show sleep LMs with time structure somewhat different from that of 'genuine' dopamine agonist responsive PLMS – as for those found in RLS/PLMD [15,20,21]. It is also well known that PLMS may occur in otherwise completely healthy subjects [55]. From these considerations, it is possible to draw a speculative interpretation of the data reported here and in the previous literature. PLMS have a strong genetic background, as demonstrated by a large genome-wide association study in Iceland [56], and appear to be an endophenotype of RLS [57]; moreover, gene variants associated with PLMS (i.e. *BTBD9* and *Meis1*) confer an increased risk for RLS [56,58]. In addition, asymptomatic PLMS herald RLS and occur more frequently in relatives of RLS patients [59] and in ethnic groups with the highest frequencies of RLS/PLMS risk alleles (eg North Americans of European vs African descent) [60]. Thus, PLMS and RLS seem to be genetically entwined [56,58]; genome-wide association studies in sporadic RLS are still finding an increasing number of genetic risk factors [61], probably characterized by a small clinical effect with their identification being possible only by recruiting a large number of cases and controls. One may speculate that the presence of these risk factors in variable combinations, in different individuals, might lead to a genetic susceptibility for presenting RLS and/or PLMS, which in turn might interact with other factors, such as the neurobiological bases of PD, to produce their final outcome. It is thus possible, if not probable, that the PDnother patients found to have PLMS in the current study with a time structure very similar to that of typical PLMS of RLS/PLMD [15,20] may be genetically predisposed for this motor phenomenon.

In conclusion, our study does not seem to support the hypothesis that PLMS are particularly frequent in PD but rather seem to indicate an interaction between PD pathophysiology and genetic predisposition for PLMS, producing a slightly increased number of patients with this sleep motor phenomenon, when compared to controls.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.03.011.

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